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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,634	04/29/2005	Bruce Ivins	4239-67021-06	5041

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,634	IVINS ET AL.	
	Examiner	Art Unit	
	EMILY M. LE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/31/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-15,18,19,37,38,40,41,50,52-57 and 61-64* is/are pending in the application.

4a) Of the above claim(s) *1-4,6-15,18,19 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,38,40,41,50,52-57 and 61-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 61-64 are added. Claims 5, 16-17, 20-36, 39, 42-49, 51 and 58-60 are cancelled. Claims 1-4, 6-15, 18-19, 37-38, 40-41, 50, 52-57 and 61-64 are pending. Claims 1-4, 6-15, 18-19 and 50 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/09/2007. Claims 37-38, 40-41, 52-57 and 61-64 are under examination. It is noted that Applicant submits that claims 37-38, 40-42, 52-57 and 61-64 are directed to the elected invention and species. However, it is found that claim 42 is cancelled. Therefore, claim 42 cannot read on the elected species.

Claim Objections

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 37-38, 40-41, 50, 52-57 and 61-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ivins et al.[1] in view of Verthelyi et al.[2] and Jones et al.[3]

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[1] Ivins et al. Recent advances in the development of an improved, human anthrax vaccine. Eur. J. Epidemiol., March 1988, Vol. 4, No. 1, p. 12-19.
[2] Verthelyi et al. CpG oligodeoxynucleotides as vaccine adjuvants in primates. The Journal of Immunology, February 15, 2002, Vol. 168, 1659-1663.

In response to the rejection, Applicant argues that it would not have been predictable that a CpG oligonucleotide comprising SEQ ID NO: 200 would enhance the immunogenicity of a vaccine against Bacillus anthracis. To support Applicant's argument, Applicant cited the teachings of Su et al. and Threadgill et al. Applicant also notes that the vaccine of Jones et al. is a simple peptide vaccine rather than a complex, multi-component vaccine such as AVA.

Applicant's argument has been considered, along with the disclosure of Su et al. and Threadgill et al., however, it is not found persuasive. Contrary to Applicant's assertion, Su et al. teaches that CpG containing oligonucleotides, such as SEQ ID NO: 200, effectively enhance the potency of a crude malaria antigen preparation (antigen) delivered in alum. Threadgill et al. also teaches that CpG containing oligonucleotides is an effective adjuvant when nonsimultaneously administered with bacterial PS vaccines. Jones et al. teaches the effective use of SEQ ID NO: 200 as an adjuvant. Applicant is reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. In the instant case, all the references acknowledge the effective use of CpG oligonucleotides as an adjuvant in vaccines.

Applicant also argues that the prior art teaches away from the claimed invention because Verthelyi et al. teaches that compared to K-type oligonucleotides, wherein SEQ ID NO: 200 is a K-type oligonucleotide, D-type oligonucleotides were superior to K-type oligonucleotides in enhancing immune response following vaccinations.

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[3] Jones et al. Synthetic oligodeoxynucleotides containing CpG motifs enhance immunogenicity of a peptide malaria vaccine in Aotus monkeys. Vaccine, 1999, Vol. 17, 3065-3071.

Applicant's argument has been considered, however, it is not found persuasive. Verthelyi et al. teaches that D-type oligonucleotide is an effective vaccine adjuvant. Verthelyi et al. also teaches that K-type oligonucleotide is an effective vaccine adjuvant. Although, Verthelyi et al. notes based on the results obtained, D type oligonucleotides may be superior vaccine adjuvants, Verthelyi et al. does not criticize, discredit or otherwise discourage the use of K-type oligonucleotides. The disclosure of more than one alternative does not constitute a teaching away from any of the alternatives unless the disclosure criticizes, discredits, or otherwise discourages the use of K-oligonucleotides.

In addition to above, Applicant argues unexpected superior results when SEQ ID NO: 200 was administered in combination with a vaccine against Bacillus anthracis compared with the vaccine alone. Applicant cited Example 4 in the specification, Klinman et al., Little et al. and Jones et al. to support the argument.

Applicant's argument has been considered, however, it is not found persuasive. Applicant's claim of unexpected superior results is expected for the administration of an adjuvant with a vaccine is predicted to enhance the immune response induced by the antigen when compared to the administration of the vaccine without an adjuvant. Regarding the teachings of Klinman et al., the reference does not evidence any unexpected results as claimed by Applicant. The entire teaching of Klinman is directed at evidencing the use of CpG oligonucleotides as an adjuvant with anthrax vaccines in rhesus macaques. While Klinman et al. demonstrates that ODN 7909, which has the same sequence as Applicant's SEQ ID NO: 200 induces greater IgG anti-PA titer than

the combination of a mixture of three different CpG oligonucleotides, when both administered with AVA vaccine, ODN 7909 had on average a 17-fold higher toxin neutralizing titer than those immunized with AVA alone; however, such is not sufficient to demonstrate or evidence unexpected results for ODN has been established as the optimal CpG oligonucleotide for human use. [Paragraph bridging left and right columns, page 2883, in particular.] The use of an optimal CpG oligonucleotide is expected to yield optimal results, as relating to adjuvant activity.

Regarding Little et al., while Little et al. teaches that alum increases antibody titer by 5-fold, this is not sufficient to demonstrate that the 17-fold increase observed by Klinman et al. is unexpected for Little et al. and Klinman et al. teaches the use of different adjuvants. Different adjuvants are expected to yield different results.

Regarding Jones et al., while Jones et al. teaches that CpG oligonucleotide increases antibody titer by 2-fold, this is not sufficient to demonstrate that the 17-fold increase observed by Klinman et al. is unexpected for Jones et al. and Klinman et al. teaches the use of different vaccines and CpG oligonucleotides. Different vaccines and oligonucleotides are expected to yield different results. Moreover, as noted above, Klinman et al. used an oligonucleotide that is known in the art to be optimal for human use.

Applicant also submits a declaration under 37 C.F.R. 1.132 by Dennis Klinman. The Klinman declaration has been considered, however, it is not found persuasive for the reason(s) provided below.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

- The nature of the fact to be sought: whether it is possible to predict if a particular class of CpG oligonucleotides will function as an effective adjuvant for a vaccine without experimental testing.
- The strength of the opposing evidence: the art, including Verthelyi et al. teaches the use of both K-type and D-type oligonucleotides as adjuvant with vaccines.
- Interest of the expert in the outcome of the case: Klinman is an inventor of the instant patent application.
- Presence or absence of factual support for the expert's opinion: The opinion is relying on the teachings of Verthelyi et al. and a summary of the results of an experiment conducted in Applicant's laboratory. Particularly, relying on Verthelyi et al., the declaration states that it is not possible to predict whether CpG oligonucleotides of the K-type or D-type class will enhance the immunogenicity of a specific vaccine with out empirical data.

To support this statement, Klinman notes that Verthelyi et al. evidences that D-type oligonucleotides, but not K-type oligonucleotides are effective when used with heat killed Leishmania vaccine. This has been considered, however, it is not persuasive. Contrary to the statement, Verthelyi et al. teaches that both K and D-type oligonucleotides are effective when used with heat killed Leishmania vaccine. Verthelyi et al. teaches the use of CpG oligonucleotides as adjuvants. In the instant case, Verthelyi et al. clearly evidences that the oligonucleotides will enhance the immunogenicity of a vaccine.

Referring to the results summarized from experiments conducted in Applicant's laboratories, the declaration also states that compared to MPL as an adjuvant, K-type CpG oligonucleotide did not significantly increase anti-influenza antibody levels or survival. The declaration notes that the results are in stark contrast with the results obtained from using the K-type SEQ ID NO: 200, which increase antibody titers by 17-fold. This has been considered, however, it is not found persuasive. Like Verthelyi et al., Applicant's results evidences the predicted use of CpG oligonucleotides, including K-type oligonucleotides as an adjuvant with vaccines.

As presented in the previous office action, the claims are directed at to a process of enhancing the immunogenicity of a vaccine comprising administering an anthrax antigen or vaccine and a CpG containing oligonucleotide having the sequence set forth in SEQ IDNO: 200 to a subject. Claim 38, which depends on claim 37, requires the

vaccine to be an antigen vaccine, a DNA vaccine, a protein subunit vaccine, a peptide vaccine, an attenuated vaccine or a heat-killed vaccine. Claim 40, which depends on claim 37, requires the antigen be from *Bacillus anthracis*. Claim 41, which depends on claim 40, requires the antigen to be a recombinant protective antigen or protective antigen. Claim 52, which depends on claim 37, requires that the oligonucleotide is administered before the vaccine is administered to the subject. Claim 53, which depends on claim 52, requires that the oligonucleotide is administered about two weeks to about one day before the vaccine is administered. Claim 54, which depends on claim 37, requires that oligonucleotide is administered concurrently with the vaccine. Claim 55, which depends on claim 37, requires that the oligonucleotide is administered after the vaccine is administered to the subject. Claim 56, which depends on claim 55, requires that the oligonucleotide is administered from about two weeks to about one day after the vaccine is administered to the subject. Claim 64, which depends on claim 37, requires the vaccine be Anthrax Vaccine Adsorbed (AVA). Claim 57 is directed to the process of claim 64. Claim 62, which depends on claim 57, requires that the administration enhances the immunogenicity of AVA by increasing IgG or IgM titer. Claim 63, which depends on claim 57, requires that the administration enhances the immunogenicity of AVA by increasing the survival of the subject upon subsequent exposure to anthrax. Claim 61 is directed at the invention of claim 41.

Ivins et al. teaches the Anthrax Vaccine Adsorbed (AVA) vaccine, which is an anthrax vaccine comprising protective antigen, which is an antigen from *Bacillus anthracis*. [Abstract, in particular.]

Ivins et al. does not teach the use of CpG oligonucleotides as an adjuvant to the vaccine. However, at the time the invention was made, it is noted that the immunity elicited by alum or aluminum hydroxide appears to be suboptimal, and suggests the use other adjuvants that may potentate immunity to anthrax. [Last paragraph, left column, page 17, in particular.]

At the time the invention was made, Verthelyi et al. establishes the use of CpG oligonucleotides as vaccine adjuvants in primates. [Title and Abstract, in particular.] Verthelyi et al. teaches that the oligonucleotides boost humoral and cellular responses, including IgG titers. Verthelyi et al. does not teach a CpG oligonucleotide having the sequence set forth in SEQ ID NO: 200, however, Jones et al. teaches an oligonucleotide having the same sequence as SEQ ID NO: 200. [Section 2, Materials and Methods, page 3066, see ODN 2006, in particular.]

Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to use the adjuvant of Jones et al. with the vaccine of Ivins et al. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to potentiate the immunity of the anthrax vaccine of Ivins et al. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the use of CpG oligonucleotides as adjuvants in primates have been demonstrated by Verthelyi et al.

Regarding the limitations of claims 52-56, which are directed to various administration protocols between the vaccine and the oligonucleotide. In the instant case, it would have been prima facie obvious for one of ordinary skill in the art to vary

the administration protocols between the vaccine and the oligonucleotide. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to optimize enhance of immunogenicity of anthrax by modifying the administration protocol. One of ordinary skill in the art, at the time the invention as made, would have had a reasonable expectation of success for doing so because the determination of a workable or optimal range and administration protocols are routinely practiced in the art.

Regarding the limitation of claim 63, which requires that the administration of the vaccine and oligonucleotide to increase the survival of the subject upon exposure to anthrax, it the instant case, such protection would inherently be provided to the subject receiving the anthrax vaccine for the essence of a vaccine is to protect a subject from exposure, including subsequent exposure.

Conclusion

4. No claims are allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/E. M. L./